Comparison of Once- Versus Twice-Daily Administration of Insulin Detemir, Used With Mealtime Insulin Aspart, in Basal-Bolus Therapy for Type 1 Diabetes

Assessment of Detemir Administration in a Progressive Treat-To-Target Trial (ADAPT)

Jean-Pierre Le Floch, MD[1]
Marc Lévy, MD[2]
Helen Mosnier-Pudar, MD[3]
Frank Nobels, MD[4]
Sylvie Laroche, MD[5]
Sophie Gonbert, MD, PHD[5]
Eveline Eschwege, MD, PHD[6]
Pierre Fontaine, MD[7]
the Assessment of Detemir Administration in a Progressive Treat-to-Target Trial (ADAPT) Study Group

OBJECTIVE — The purpose of this study was to compare effects of insulin detemir once daily versus twice a day in a basal-bolus insulin regimen.

RESEARCH DESIGN AND METHODS — In this open-label, 7-month study, 520 patients with type 1 diabetes were randomly assigned to receive detemir once daily or twice daily with mealtime insulin aspart. Insulin doses were titrated over 1 month, with patients followed up over the subsequent 3 months. Thereafter, patients were able to switch from one regimen to the other, with an additional nonrandomized 3-month follow-up, to a total of 7 months. The primary end point was A1C at 4 months, with noninferiority defined as a difference <0.4% between groups.

RESULTS — A1C at 4 months was 8.1 ± 0.9 versus 8.0 ± 1.0% with once- and twice-daily detemir, respectively, with an adjusted between-group difference of 0.12% (95% CI −0.01 to 0.25%), showing noninferiority for once-daily dosing. Similar results were found in the per protocol population. Improvement in A1C was similar in both groups (−0.4 ± 0.8 vs. −0.5 ± 0.8%; $P = 0.09$, NS) but with differences in the 7-point glucose profile. Detemir doses were lower (29 ± 18 vs. 39 ± 20 units/day, $P < 0.001$), but aspart doses were higher (34 ± 17 vs. 26 ± 14 IU/day, $P < 0.001$) with once-daily detemir. At 7 months, A1C decreased slightly in patients switched from once-daily to twice-daily administration (8.2 ± 0.8 vs. 8.0 ± 0.8%; $P = 0.34$, NS) in association with increased total insulin doses ($P < 0.05$), but A1C increased in those switched from twice-daily to once-daily administration (7.2 ± 0.9 vs. 7.6 ± 0.8%, $P < 0.05$) in association with decreased doses ($P < 0.05$).

CONCLUSIONS — Although some individuals may benefit from twice-daily dosing, the most suitable routine starting schedule for detemir in a basal-bolus regimen for type 1 diabetes is once-daily injection.

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From the [1]Medical Clinic, Villecresnes, France; the [2]Max Fourestier Hospital, Nanterre, France; the [3]Cochin Hospital, Paris, France; the [4]OL Vrouwziekenhuis Hospital, Aaslt, Belgium; [5]Novo Nordisk Pharmaceutics, Paris, France; [6]Institut National de la Santé et de la Recherche Médicale U780, Villejuif, France; and the [7]Clinique Marc Linquette, Lille, France.
Corresponding author: J.P. Le Floch, jplefloch@dietvill.com.
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The basal insulin analog insulin detemir (detemir) differs from human insulin by a single amino acid deletion and the acylation of myristic acid to the B terminus of the molecule. These changes affect the pharmacokinetics of the insulin, prolonging absorption from a subcutaneous depot through a unique mechanism involving self-association of detemir molecules and reversible binding to albumin (1). The result is a more prolonged, less peaked absorption (and hence pharmacodynamic) profile compared with that of NPH insulin (NPH) (2). Another property of detemir, believed to result from albumin binding, is reduced intrasubject variability of the pharmacodynamic profile (3) compared with those of both NPH (4,5) and insulin glargine (4,6). In theory, reduced intrasubject variability should reduce the risk of hypoglycemia (4,7). This theory was confirmed clinically in comparative trials against NPH involving basal-bolus therapy in type 1 diabetes in which detemir demonstrated similar efficacy but consistent reductions in the frequency of hypoglycemia during the night, when the absence of mealtime bolus insulin unmasks differences in the pharmacodynamics of basal insulins (8). Detemir has also been consistently associated with reduced weight gain compared with NPH (9).

Most initial studies of detemir in type 1 diabetes involved a twice-daily regimen, but recent pharmacological analyses (6,7) suggest that detemir has a pharmacodynamic profile similar to that of insulin glargine, a basal insulin that is routinely injected once daily. Using a standard definition for duration of action, detemir has been reported to endure for a mean of close to 24 h in type 1 diabetes and longer in type 2 diabetes (7). In addition, data from the large-scale observational Predictable Results and Experience in Diabetes through Intensification and Control to

Target: An International Variability Evaluation (PREDICTIVE) study show that a majority of patients have been using detemir once daily and achieving clinically important improvements in glycemic control (10), although this was not a comparative trial. A recent analysis of basal insulin studies by DeVries et al. (11) suggested that, although a percentage of patients may benefit from twice-daily basal insulin dosing, the routine use of twice-daily basal regimens tends to drive up the total unit dose of insulin without corresponding gains in glycemic control. These observations call into question the routine of twice-daily dosing of detemir in most patients. The present study is the first specifically designed to assess whether routine use of twice-daily detemir in basal-bolus therapy for type 1 diabetes offers any clinical advantages over once-daily administration.

RESEARCH DESIGN AND METHODS

The Assessment of Detemir Administration in a Progressive Treat-to-Target Trial (ADAPT) was an open-label study performed at centers in Belgium (6) and France (193). It comprised a randomized 4-month, parallel-group period comparing once-daily with twice-daily detemir, followed by a nonrandomized 3-month extension period at the beginning of which crossover was permitted.

Included were patients with type 1 diabetes diagnosed for >1 year and with A1C 7.5–10%, regardless of their prestudy insulin regimen. Exclusion criteria included likelihood of pregnancy, use of oral antidiabetes drugs, hypoglycemia unawareness, severe degenerative complications or associated disease, and associated drugs or conditions capable of altering glucose control. Withdrawal criteria included serious adverse events, pregnancy, the necessity of stopping study treatment, and major protocol deviation as judged by a study committee.

For the randomized part of the study, patients were assigned to either once-daily (at bedtime) or twice-daily (before breakfast and at bedtime) injections of detemir, with bolus doses of insulin aspart (aspart) given three times daily at mealtimes. The randomization list was generated by computer using an aleatory function before the start of the trial and the Interactive Voice Response telephone randomization system. Both insulins were supplied in 100 units/ml 3-ml FlexPen devices (Novo Nordisk, Copenhagen, Denmark).

After 1 month of intensive titration, patients were followed up over 3 more months, with primary end points being evaluated at the end of this period. Dosing guidelines were developed to facilitate titration and switching patients to the new insulin regimen from previous insulin therapy. Initial doses of detemir were to equal previous basal insulin doses, either injected at bedtime (once-daily group) or half before breakfast and half at bedtime (twice-daily group). The initial dose of mealtime aspart was to equal the mealtime insulin doses used previously. If <3 mealtime injections were given previously, the new injections were begun at 4 IU.

Subsequent titration was at the discretion of investigators and patients, but guidelines were provided: detemir doses were to be titrated against fasting glucose values in the once-daily group and against fasting and predinner glucose values in the twice-daily group. Detemir was to be increased by 6 units if the mean glucose concentration at these times over the 3 preceding days was >180 mg/dl, by 4 units if 180–165 mg/dl, by 3 units if 165–145 mg/dl, and by 2 units if 145–120 mg/dl. Detemir was decreased by 4 units if unexplained glucose values <50 mg/dl were observed and by 2 units if values of 50–72 mg/dl were seen. Aspart was to be increased by 6 IU if mean postprandial glucose values over the 3 preceding days, measured 1–1.5 h after meals, were >270 mg/dl, by 4 IU if 200–270 mg/dl, and by 2 IU if 180–200 mg/dl.

At the end of the 4-month randomized period, the basal dosing schedule was allowed to be switched at the discretion of investigators and patients, although the following guidelines were provided: switching from once-daily to twice-daily detemir was advised if the 4-month A1C was >7.5% (the European guideline target at the time of trial registration) or most predinner glucose values were >120 mg/dl. Switching from twice-daily to once-daily detemir was advised only when A1C was <7.5%, the fasting detemir dose was <6 units, and most predinner glucose values were <120 mg/dl.

Visits were made at inclusion (baseline) and at 4 and 7 months. Telephone contact was made weekly during the first month and then at 7, 10, 19, and 22 weeks.

A1C was determined centrally (Focus Bio-Inova Europe) by high-performance liquid chromatography (Bio-Rad Variant II kit). Self-measurement of blood glucose, for construction of 7-point glycemic profiles, was requested to be made before and after (1–1.5 h) meals and at bedtime for each of the 14 days before the 4-month follow-up period.

Hypoglycemic episodes were classified as "major" if assistance was required, as "minor" if blood glucose readings <2.8 mmol/l (0.5 g/l) were recorded but patients were able to deal with the episodes themselves, or as "symptoms only" if hypoglycemic symptoms were reported without a confirmed blood glucose measurement. Hypoglycemia was documented over 24 h, and incidences of hypoglycemia were based on events recorded in the last 14 days before each main visit.

Statistical analyses

The primary end point was A1C at 4 months, with a noninferiority analysis performed using ANCOVA adjusted for baseline. Noninferiority was defined before the study using the criterion agreed on between Novo Nordisk and the U.S. Food and Drug Administration (FDA) for the detemir phase 3 study program, namely, a difference in A1C between groups of <0.4% A1C (12).

Secondary end points were analyzed with ANOVA, ANCOVA, or the Wilcoxon test for quantitative variables and a χ^2 or Fisher's exact test for qualitative ones. SAS software (version 8.2; SAS Institute, Cary, NC) was used. Analyses were performed using the last observation carried forward method. Unless otherwise stated, results are shown as means ± SD or percent. Insulin dose data are presented as total units, but similar results were found using units per kilogram.

Because the extension period (4–7 months) was uncontrolled with unequal cohort numbers, results at 7 months are presented without statistical analyses between groups. Within-subject comparisons (4 vs. 7 months) are presented for clinical interest in real-life situations but should be considered with caution.

RESULTS

Disposition

A total of 520 patients were included and randomly assigned, of whom 8 did not take treatment; hence, the intent-to-treat population included 512 patients (250

once-daily detemir and 262 twice-daily detemir). Major protocol deviations were observed in 29 and 26 patients taking once-daily detemir (12%) and twice-daily detemir (10%), respectively ($P = 0.34$, NS). The most common deviations were no respect for randomization (16 patients; 3.1%), delayed baseline A1C assay (14 patients; 2.7%), and A1C outside the inclusion range (4 patients; 0.8%). Five patients (1.0%) randomly assigned to once-daily detemir switched without consultation to twice-daily detemir. Twenty-three patients withdrew from the trial because of poor glycemic control (10 vs. 5 taking once-daily vs. twice-daily detemir, respectively, $P < 0.05$) or discomfort (2 taking once-daily vs. 6 taking twice-daily detemir, respectively, $P < 0.05$). All patients with major protocol deviations were excluded from the per protocol population.

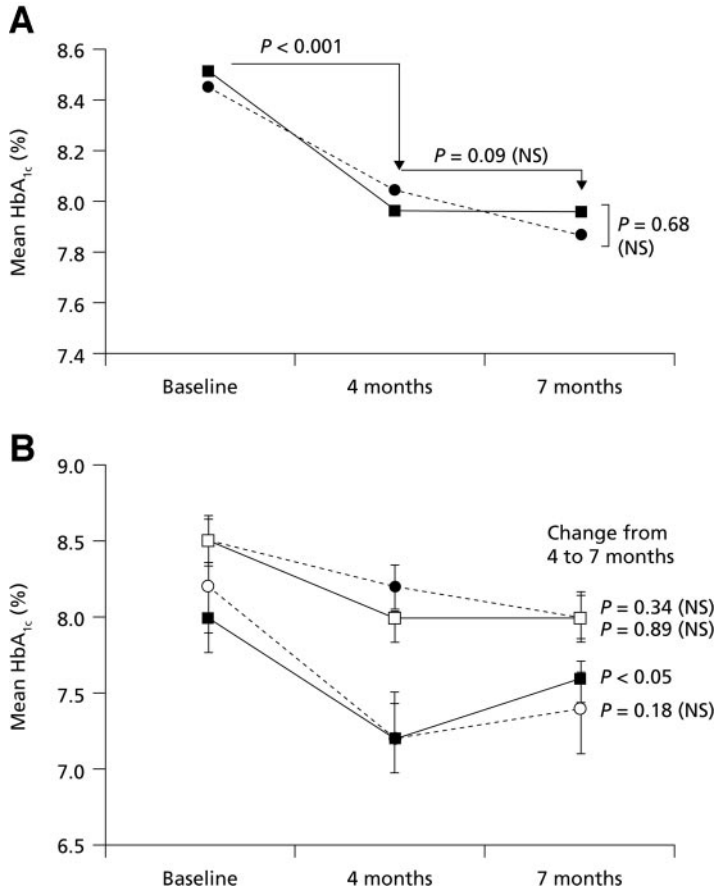

Figure 1—A: *A1C values at baseline and at 4 and 7 months according to the original randomization group.* ●, *patients originally randomized to once-daily detemir;* ■, *patients originally randomized to twice-daily detemir.* B: *A1C values at baseline and at 4 and 7 months according to the original and final basal dosing frequency. Error bars show SD.* ○, *patients staying on once-daily detemir after 4 months;* ●, *patients switching from once- to twice-daily detemir at 4 months;* □, *patients staying on twice-daily detemir after 4 months;* ■, *patients switching from twice- to once-daily detemir at 4 months.*

Demographics

At inclusion, there were no between-treatment differences between the once-daily and twice-daily detemir groups regarding sex (53 vs. 52% men, respectively, $P = 0.74$, NS), age (41 ± 13 vs. 42 ± 13 years, $P = 0.32$, NS), BMI (25 ± 4 vs. 25 ± 4 kg/m^2, $P = 0.08$, NS), duration of diabetes (16 ± 10 vs. 17 ± 10 years, $P = 0.40$, NS), frequency of degenerative complications (40 vs. 44%, $P = 0.41$, NS), previous insulin doses (52 ± 20 vs. 51 ± 19 IU/day, $P = 0.79$, NS), number and type of insulin injections (two or three injections 17 vs. 16%, median four injections 70 vs. 72%, five or six injections 13 vs. 12%, $P = 0.88$, NS), A1C (8.5 ± 0.8 vs. 8.5 ± 1.0%, $P = 0.71$, NS), and hypoglycemia frequency during the preceding 2 weeks (3.3 ± 3.6 vs. 3.6 ± 4.0, $P = 0.60$, NS). Associated diseases were less frequent in the once-daily detemir group (54 vs. 64%, $P < 0.05$) because of a lower frequency of treated hypothyroidism (2.4 vs. 5.4%, $P < 0.05$).

After randomization, suggested total insulin doses proposed by the investigators were similar in the once-daily and twice-daily detemir groups (respectively, detemir 27 ± 12 vs. 27 ± 12 units/day, $P = 0.46$, NS; aspart 25 ± 12 vs. 23 ± 12 IU/day, $P = 0.64$, NS). Twice-daily detemir was injected at a similar dose before breakfast and at bedtime (14 ± 6 and 14 ± 6 units/day, $P = 0.92$, NS). Aspart doses were slightly higher with once-daily detemir (breakfast 7 ± 4 vs. 7 ± 4 IU/day, $P = 0.06$, NS; lunch 9 ± 4 vs. 8 ± 4 IU/day, $P < 0.05$; dinner 9 ± 5 vs. 9 ± 5 IU/day, $P = 0.11$, NS).

Clinical outcomes

A1C data are summarized in Fig. 1. At 4 months, A1C was similar in the once-daily and twice-daily groups (8.1 ± 0.9 vs. 8.0 ± 1.0%), with an adjusted between-group difference of 0.12% (95% CI −0.01 to 0.25; post hoc power 95%), thereby showing noninferiority for once-daily dosing. Similar results were found in the per protocol population (adjusted difference 0.13%, 95% CI −0.01 to 0.26; power 92%). A1C was <7.0% in 14.2% of patients taking once-daily detemir and 15.6% of patients taking twice-daily detemir ($P = 0.67$, NS). Improvement of A1C was similar in both groups (−0.4 ± 0.8 vs. −0.5 ± 0.8%; $P = 0.09$, NS). At 4 months, capillary blood glucose levels were lower with once-daily detemir before breakfast ($P < 0.0001$) but higher before and after other meals ($P < 0.02$) (Fig. 2).

There was a slight change in BMI with both once-daily and twice-daily detemir (0.2 ± 0.8 vs. 0.2 ± 1.0 kg/m^2, $P = 0.83$, NS). The frequency of hypoglycemia over the 4-month randomization period was similar in both groups (21 ± 16 vs. 24 ± 24 events per patient per 14 days, $P = 0.47$, NS) and did not differ by classification of severity. No differences were seen in the pattern of other adverse events by group. Both regimens were well tolerated, with most adverse events not considered to be related to the study drugs.

Insulin dose

Total insulin doses were similar with once-daily and twice-daily detemir (62 ± 31 vs. 64 ± 29 units/day, respectively, $P = 0.34$, NS), but detemir doses were lower with once-daily dosing (29 ± 18 vs.

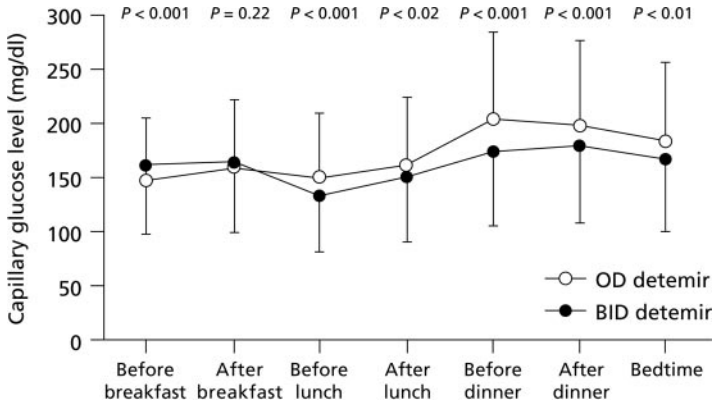

Figure 2—*Capillary glucose profiles at 4 months in once-daily (OD) and twice-daily (BID) detemir groups. Mean glucose levels are shown, with error bars representing SD.*

39 ± 20 units/day, $P < 0.001$). Conversely, aspart doses were higher with once-daily detemir (34 ± 17 vs. 26 ± 14 IU/day, $P < 0.001$ [breakfast 9 ± 6 vs. 7 ± 5, $P < 0.01$; lunch 11 ± 6 vs. 8 ± 4, $P < 0.001$; dinner 14 ± 7 vs. 11 ± 7, $P < 0.001$]).

Nonrandomized 4- to 7-month follow-up

After the 4-month randomized period, most patients continued in the study with twice-daily detemir (172 from the once-daily group and 226 from the twice-daily group), with 33 patients (13%) remaining with once-daily detemir and 10 (4%) switching from twice-daily to once-daily detemir. No differences in baseline demographics or disease characteristics were detected between patients staying with once-daily detemir or switching to twice-daily detemir or between patients staying with twice-daily detemir or switching to once-daily detemir. A1C values at 4 and 7 months by actual detemir regimen are shown in Fig. 1*B*. In patients staying with once-daily detemir, A1C was 7.2 ± 0.9% at 4 months, remaining steady until 7 months at 7.4 ± 0.9% ($P = 0.18$, NS, before versus after switching). For patients switching from once-daily to twice-daily detemir, A1C was 8.2 ± 0.8 and 8.0 ± 0.8%, respectively, at 4 and 7 months ($P = 0.34$, NS, before versus after switching). A1C remained steady between 4 and 7 months in patients remaining with twice-daily detemir (8.0 ± 1.0 and 8.0 ± 1.1%, $P = 0.89$), but for those switching from twice-daily to once-daily detemir, A1C increased from 7.2 ± 0.9 to 7.6 ± 0.8% ($P < 0.05$, before versus after switching, respectively).

Insulin dose data at 4 and 7 months are presented by actual basal insulin regimen in Fig. 3. There were very slight increases in total insulin dose among patients remaining with their original regimens (once-daily $P = 0.76$, NS; twice daily $P = 0.64$, NS), a small increase in patients switching from once-daily to twice-daily detemir ($P < 0.05$), and a marked decrease in patients switching from twice-daily to once-daily detemir ($P < 0.05$).

CONCLUSIONS — Most previous clinical trials of detemir given in basal-bolus therapy for type 1 diabetes used a twice-daily dosing schedule. One study allowed once- or twice-daily dosing (13), and another used only once-daily detemir dosing but with regular human insulin given instead of a rapid-acting analog at mealtimes (14). The use of once-daily detemir in basal-bolus therapy is therefore not well documented by trial data; yet, pharmacodynamic evidence suggests suitability for this more convenient schedule (7).

This is the first study to compare once-daily and twice-daily regimens of detemir as the basal component of basal-bolus therapy in a randomized trial design. The patients studied were adults with type 1 diabetes, diagnosed for >1 year, i.e., with little or no endogenous insulin secretion, making this a valid test system for differences in clinical end points attributable to differences in basal insulin regimen. Furthermore, baseline glycemic control of patients was poor despite the fact that the great majority were using basal-bolus therapy; hence, the cohort can be regarded as a stringent one in which to evaluate once-daily detemir dosing. The 4-month results suggest that, on average, a twice-daily dosing schedule has no clinically significant advantage over once-daily dosing. Mean A1C (Fig. 1*A*) and the percentage of patients reaching A1C <7.0% were not significantly different between dosing groups at this time, whereas basal and (to a lesser extent) overall insulin doses were shifted upward with twice-daily dosing, consistent with the observations of DeVries et al. (11). This dose-shifting effect was also apparent upon switching from once-daily to twice-daily detemir (Fig. 3). Our randomized 4-month data therefore suggest that routine use of detemir in a twice-daily regimen is unnecessary: once-daily detemir should be regarded as the routine standard regimen.

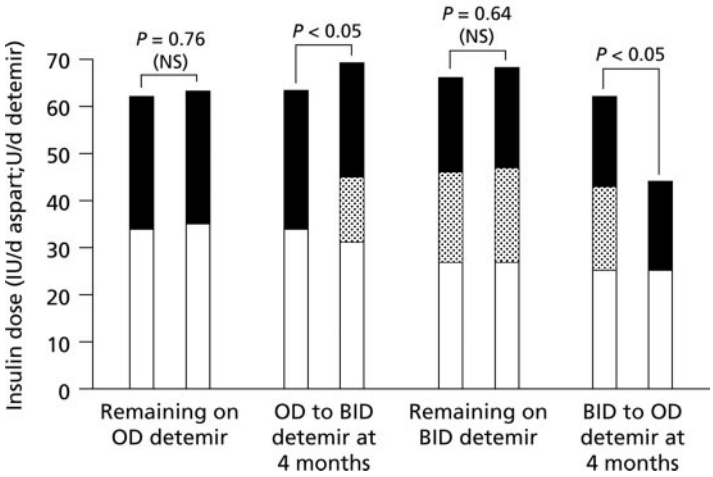

Figure 3—*Detemir and aspart doses after 4 and 7 months in four groups of patients. Significant changes of total insulin doses (4 vs. 7 months; P < 0.05) were observed for patients switching from once-daily (OD) to twice-daily (BID) and from twice daily to once-daily detemir. Significance represents the change in total insulin dose. □, total aspart; ▨, detemir at breakfast; ■, detemir at bedtime. d, day.*

It should be noted, however, that there was a small excess of noncompleters because of poor efficacy in the once-daily group and that differences were detected in mean diurnal blood glucose profiles at 4 months (Fig. 2), with glucose tending to be lower before breakfast but rising to higher levels later in the day after once-daily evening dosing. These observations are again consistent with those described by DeVries et al. (11) with regard to studies of insulin glargine (15–17). As these glycemic profiles depict mean values, the implication is that some individuals will show a more extreme rise in glucose when treated with once-daily detemir, and it might be better for such individuals to be switched to twice-daily dosing. Again, this scenario has been described previously in studies involving insulin glargine (15,17,18).

When the 7-month follow-up data are considered in terms of original groups, there is little change (Fig. 1*B*), supporting the view that once-daily dosing is an appropriate routine starting regimen for detemir. However, this trial was not a randomized crossover study. The glycemic criteria by which crossovers were recommended biases subsequent results in favor of twice-daily dosing because poor responders to once-daily dosing were encouraged to switch to twice-daily dosing, whereas only good responders to twice-daily dosing were encouraged to switch to once-daily dosing. Evidence that this was indeed the case is provided in Fig. 1*B*, where it is noteworthy that patients remaining with once-daily dosing had a much lower 4-month A1C than those switching to twice-daily dosing. Conversely, patients switching from twice-daily to once-daily dosing had a much lower 4-month A1C than those remaining with once-daily dosing. Interestingly, although there was a tendency for A1C to decrease over months 4–7 in patients switched from once-daily to twice-daily dosing, the magnitude of change was small and (at 0.2% A1C) beneath the a priori criterion agreed on with the FDA for clinical significance. The patients with good glycemic control taking twice-daily detemir who switched to once-daily dosing at 4 months showed an increase in A1C of a magnitude deemed clinically significant (0.4%, $P < 0.05$). Nevertheless, the 7-month A1C in this cohort (7.6%) was lower than that of patients who remained with twice-daily dosing throughout and lower than that of the cohort who switched from once-daily to twice-daily dosing. It must also be noted that there was a marked decrease in total insulin dose in patients switching from twice-daily to once-daily detemir, with the morning basal dose removed and the evening dose apparently not sufficiently increased to compensate (Fig. 3). Taken altogether, these observations again support once-daily dosing as an efficient standard regimen for initiating detemir, although the slight reversal in patients' A1C after switching again suggests the existence of a small subset of patients who do benefit from twice-daily dosing.

A limitation of our study is the open-label design, chosen to avoid a complicated double-dummy injection schedule. This design is likely to have influenced the high frequency of switching from once-daily to twice-daily detemir at the completion of the randomized phase. After the opportunity to switch at 4 months, 28% of patients taking once-daily detemir had A1C <7.5%, yet only 13% elected to stay with this regimen. It is likely that patients and investigators may have had the preconception that a twice-daily regimen would achieve better glycemic control; however, switching from once-daily to twice-daily dosing, on average, yielded only marginal improvement. Arguably, another limitation of our study is that the data need to be viewed in the context of glycemic control falling short of modern guideline targets. Although guidelines were given, titration was largely carried out at the discretion of patients and investigators; hence, this study cannot be considered a treat-to-target study. For instance, patients switching from twice-daily to once-daily dosing did not tend to compensate for the immediate basal insulin dose reduction. However, the cohort studied were patients with type 1 diabetes with poor baseline glycemic control (A1C 8.5%), despite the use of multiple-injection (four to six injections per day) therapy, so mean improvement of 0.4–0.5% over 4 months may not fall short of realistic clinical expectations.

In summary, this study demonstrates the overall noninferiority of once-daily dosing based on a priori criteria when detemir is used in basal-bolus therapy for type 1 diabetes. The data do, however, also suggest the existence of a subset of patients who will benefit from twice-daily dosing, as has also been demonstrated in studies of insulin glargine (15–17). Thus, in individual patients in whom a poor overall response is seen with high predinner blood glucose values, adding a second dose of detemir, as is the case for all other basal insulins, is worth considering. As a standard regimen, however, detemir should be given once daily in the basal-bolus therapy of patients with type 1 diabetes because, on average, this leads to similar A1C with reduced injection frequency.

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References

1. Havelund S, Plum A, Ribel U, Jonassen I, Vølund A, Markussen J, Kurtzhals P: The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. *Pharm Res* 21:1498–1504, 2004
2. Plank J, Bodenlenz M, Sinner F, Magnes C, Görzer E, Regittnig W, Endahl LA, Draeger E, Zdravkovic M, Pieber TR: A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care* 28:1107–1112, 2005
3. Kurtzhals P: How to achieve a predictable basal insulin? *Diabetes Metab* 31(4 Pt 2): 4S25–4S33, 2005
4. Heise T, Nosek L, Rønn BB, Endahl L, Heinemann L, Kapitza C, Draeger E: Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 53:1614–1620, 2004
5. Wutte A, Plank J, Bodenlenz M, Magnes C, Regittnig W, Sinner F, Rønn B, Zdravkovic M, Pieber TR: Proportional dose-response relationship and lower within-patient variability of insulin detemir and NPH insulin in subjects with type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 115:461–467, 2007
6. Klein O, Lynge J, Endahl L, Damholt B, Nosek L, Heise T: Albumin-bound basal insulin analogs (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 di-

abetes. *Diabetes Obes Metab* 9:290–299, 2007
7. Heise T, Pieber TR: Towards peakless, reproducible and long-acting insulins: an assessment of the basal analogs based on isoglycemic clamp studies. *Diabetes Obes Metab* 9:648–659, 2007
8. Home P, Kurtzhals P: Insulin detemir: from concept to clinical experience. *Expert Opin Pharmacother* 7:325–343, 2006
9. Hermansen K, Davies M: Does insulin detemir have a role in reducing risk of insulin-associated weight gain? *Diabetes Obes Metab* 9:209–217, 2007
10. Dornhorst A, Lüddeke HJ, Sreenan S, Koenen C, Hansen JB, Tsur A, Landstedt-Hallin L: Safety and efficacy of insulin detemir in clinical practice: 14-week follow-up data from type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. *Int J Clin Pract* 61:523–528, 2007
11. DeVries JH, Nattrass M, Pieber TR: Refining basal insulin therapy: what have we learned in the age of analogs? *Diabetes Metab Res Rev* 23:441–454, 2007
12. Tsou HH, Hsiao CF, Chow SC, Yue L, Xu Y, Lee S: Mixed noninferiority margin and statistical tests in active controlled trials. *J Biopharm Stat* 17:339–357, 2007
13. Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall MA, Ludvigsson J: Insulin detemir compared with NPH insulin in children and adolescents with type 1 diabetes. *Diabet Med* 24:27–34, 2007
14. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J: Effects of OD insulin detemir or neutral protamin hagedorn on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus insulin regimen. *Clin Ther* 26:724–736, 2004
15. Albright ES, Desmond R, Bell DS: Efficacy of conversion from bedtime NPH insulin injection to once- or twice-daily injections of insulin glargine in type 1 diabetic patients using basal/bolus therapy. *Diabetes Care* 27:632–633, 2004
16. Ashwell SG, Gebbie J, Home PD: Optimal timing of injection of once-daily insulin glargine in people with type 1 diabetes using insulin lispro at meal-times. *Diabet Med* 23:46–52, 2006
17. Ashwell SG, Gebbie J, Home PD: Twice-daily compared with once-daily insulin glargine in people with type 1 diabetes using meal-time insulin aspart. *Diabet Med* 23:879–886, 2006
18. Garg SK, Gottlieb PA, Hisatomi ME, D'Souza A, Walker AJ, Izuora KE, Chase PH: Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine. *Diabetes Res Clin Pract* 66:49–56, 2004